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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/791,240	01/30/1997	ALEXANDER J. RYNCARZ	BDI-1020	2505

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EXAMINER

SISSON, BRADLEY L

ART UNIT

PAPER NUMBER

1634

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43

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No.	Applicant(s)
	08/791,240	RYNCARZ, ALEXANDER J.
	Examiner Bradley L. Sisson	Art Unit 1634

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1) Responsive to communication(s) filed on 11 March 2002.

2a) This action is **FINAL**.      2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4) Claim(s) 1-52 and 59-65 is/are pending in the application.

4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.

5) Claim(s) \_\_\_\_\_ is/are allowed.

6) Claim(s) 1-52 and 59-65 is/are rejected.

7) Claim(s) \_\_\_\_\_ is/are objected to.

8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on \_\_\_\_\_ is: a) approved b) disapproved by the Examiner.  
 If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
 a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)
3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____	6) <input type="checkbox"/> Other: _____

## **DETAILED ACTION**

### ***Location of Application***

1. The location of the subject application has changed. The subject application is now located in Group 1630, Art Unit 1634.

### ***Withdrawal of Finality***

2. The finality of the prior Office action is hereby withdrawn. Prosecution on the merits is reopened.

### ***Specification***

3. Claim 21 objected to because of the following informalities: The hard return at the end of line 2 needs to be deleted. Appropriate correction is required.

### ***Claim Objections***

4. Claim 62 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 1 requires that the first primer be extended when bound to the target sequence. Consequently, it is less than clear how claim 62 further limits claim 1 from which it depends.

***Claim Rejections - 35 USC § 112***

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-57 and 59-65 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As presently worded, the method of said claims encompasses the amplification of a target sequence (DNA, RNA, chimeric sequences, as well as modified nucleotides) of virtually size and the use of a primer of no minimum size and the use of an exonuclease, be it separate or integral to the polymerase. Such scope of claims encompasses the degradation of the template and/or the primer used to amplify same. While the claims have been limited in part to where a primer is added or included wherein said primer has a mismatch at the 3' terminus and encompasses modified nucleotides that are resistant to exonuclease activity, such only goes to preserve the presence of a non-extendable primer that cannot be used in the amplification of a target sequence.

7. The specification is essentially silent as to how one is to amplify RNA or to generate RNA amplicons from a DNA template, in combination with the use of an RNA exonuclease and RNA polymerase. It is noted that in the case of claim 50, the template has been limited to DNA.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-52 and 59-65 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claim 1 is confusing where in line 1 it is stated that there is "a target sequence." The use of "a" is considered to imply that there is but one target sequence. In line 8, however, it is now indicated that the amplification products are "copies of the target sequence." Seemingly if here is but one target sequence, then only one of primers used will result in an amplification of said target sequence, the other primer will be useful in the generation of the complement of the target sequence. If both primers are to give rise to an amplified target sequence, then the "sequence" is to be construed as if it were being used in the plural, and then the aspect of a "second polynucleotide" (line 9) would then be a third sequence. Alternatively, if only one primer gives rise to an amplified target (even though the claim seems to suggest that both primers do), and the second primer is to give rise to the amplification of the complementary sequence, then seemingly there would be asymmetric amplification of the target sequence. Claims 2-8, which depend from said claim 1, fail to overcome this issue and are similarly rejected.

11. Claims 3, 9, 26, 40 are confusing as to what constitutes "fully complementary" and how that differs from "complementary."

12. Claim 9, and the claims that depend therefrom, are indefinite with respect to how a first primer can, in essence, hybridize to self. Attention is directed to claim 9, step (b) which reads in pertinent part:

(b) extending, in the presence of a polymerase having 3'; to 5' exonuclease activity, said first primer along at least said target sequence, said first primer being capable of hybridizing to, and being extended along, (1) said extended first primer.... (Emphasis added)

Similarly, it is unclear how one is to extend an extended first primer with said first primer (see step (e)).

13. Claim 9 is confusing when read in the context of claim 23. Claim 23 states that the first and second primers are to be “different” which, for purposes of examination has been interpreted as meaning that they are different from one another. Given that all dependent claims are to further limit the independent claim from which they depend, the aspect of requiring the first and second primers in claim 23 to be “different” reasonably suggests that the first and second primers in claim 9 are not required to be different. It is unclear how the method of claim 9 is to be practiced when the “first” and “second” primers are the same. Claims 10-22 and 24 are also rejected as they fail to overcome this issue.

14. Claims 4 and 41 are indefinite with respect to what constitutes the metes and bounds of “substantially identical.” Claims 5 and 6, which depend from claim 4; and claim 41, which depends from claim 41, fail to overcome this issue and are similarly rejected.

15. Claims 23 and 24 are indefinite with respect to what the primers are “different.”

16. Claim 25 is confusing with respect to what is the “control primer.” As the claim present reads, it is clear that there is a “primer A,” and a “primer B” and reference is made to a “control primer.” However, it is not clear if primer A or primer B is the control primer or whether a third primer is present

17. Claim 39 is indefinite with respect to the metes and bounds of “partially sequentially” (see line 14).

18. Claims 59 and 60 are confusing as to how the reaction is “further controlled.” While one may use an exonuclease to remove mismatched nucleotides from the 3'-terminus of a primer so that primer extension may proceed, it is unclear how such actions constitute “further control.”
19. Claim 63 is confusing, as it appears to be an incomplete sentence.

***Claim Rejections - 35 USC § 103***

20. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

21. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

22. Claims 1-3, 7-10, 14-26, 30-40, 44--52, 59, 60, and 62-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sorenson (WO 93/22456), Gelfand et al. (US Patent 5,491,086), and Barnes (US Patent 5,436,149).

23. Sorenson disclose a method of detecting an amplification of polynucleotide sequences wherein said method comprises the use of a plurality of primers that vary at their 3' terminus. Only those primers that are fully complementary with the target sequence will undergo or

participate in the amplification reaction. See page 11. The aspect of having other, non-complementary sequences present in the assay is considered to meet the limitation of having a positive control present.

24. Sorenson does not disclose using exonuclease activity, be it an inherent aspect of the polymerase being used or be it added separately.

25. Gelfand et al., column 26, disclose the use of a DNA polymerase with 3' to 5' exonuclease activity. The use of such a polymerase, and especially in conjunction with primers that have a 3' mismatch is considered to render obvious the use of an exonuclease in conjunction with performing an amplification reaction whereby one or more primers are used and that said primers are designed to contain a mismatch at the 3' terminus.

26. Gelfand et al., does not teach the addition of an exonuclease in combination with a polymerase.

27. Barnes, column 17, discloses adding an exonuclease to their amplification reactions so to remove the mismatch that may be present at the 3' terminus of their primers.

28. It would have been obvious to one of ordinary skill in the art at the time the invention was made to have combined the use of multiple primers, at least some of which have 3' mismatch sequences at the 3' terminus (Sorenson) with the use of an exonuclease, be it added directly or an inherent property of the polymerase being used, whereby the mismatch is removed from non-complementary primers and thereby allowing for the amplification of one or more sequences.

29. In view of the well developed nature of the art, and the explicit teaching of using primers with a 3' mismatch and the use of exonucleases so to remove this mismatch so to allow for an

amplification reaction to proceed, the ordinary artisan would have been highly motivated to have combined such and would have had a reasonable expectation of success that the assay would have been functional and useful. The aspect of performing the amplification step but three times, or to have a positive control of a certain size range, or to use reactants at one or more concentrations are all considered to be the results of routine experimentation as a review of the disclosure fails to find support for where these aspects are considered by applicant to constitute the invention or lend patentable weight to the claimed method.

### *Conclusion*

30. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is 703-308-3978. The examiner can normally be reached on Monday through Thursday from 6:30 AM to 5 PM.
31. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on 703-308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

32. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234.



Bradley L. Sisson  
Primary Examiner  
Art Unit 1634

BLS  
May 19, 2002



W. Gary Jones  
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